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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,050	10/12/2004	Masami Kusaka	Q101060	6207

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,050	KUSAKA ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 5-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-3 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of amended claims and RCE filed on 08/11/08 is acknowledged.

Claims **2-3 and 5-7** are under prosecution.

Unless specifically repeated, the rejections made in previous office action have been withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

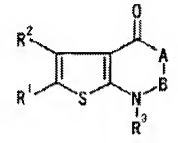
Scope of Enablement Rejection

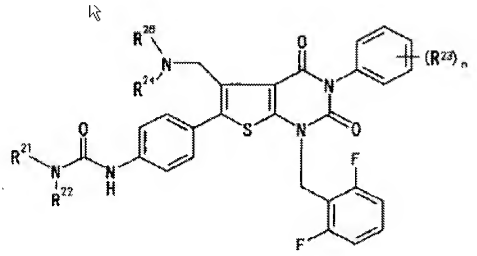
Claims **2-3 and 5-7** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of compounds of the formula, does not reasonably provide enablement for the trillions of possible structures claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to *make and use* the invention commensurate in scope with these claims. For instance, with respect to the *making* aspect of the invention, of the multiple possibilities for R1 and R2 and R3 and p and q groups in claim 5 and several substituents in claim 6, the specification is enabling for the making of one possibility. Likewise, in support of the biological activity of the claimed compounds (i.e., *potential* utility), the disclosure is limited to describing only single possibility of single compound with specific substituents linked to treating hot flashes.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: The claims are drawn to compounds of the formula *(elected group),*





With multiple possibilities of substituents as disclosed in claims 5 and 6.

The side groups having substituents layered on top of substituents encompassing trillions of possible compounds. The substituents vary widely in size, molecular topology, properties such as acidity and basicity chemical and physical properties rendering the breadth of the claims wide. The disclosure lacks guidance linking various possible substituents with hot flashes. No technical data has been provided and with no effective amounts have been recited in claims. In the absence of specific compounds or groups of compound, specific effective amount and their correlation with hot flashes, one skill in the art would undergo undue experimentation to practice the invention. In the absence of any specific amount associated with specific compound, the claim reads on indefinite amounts or very miniscule amount which will be required to treat hot flashes.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic and medicinal chemistry, it is noted that each

embodiment of the invention is required to be individually assessed for viability.

The amount of direction provided by the inventor and the presence or absence of working examples: The direction and working example provided in the specification is extremely limited.

Specification only provides compound on page 33 and it is not seen where in the specification, enablement is present for making any other substituents for these three variables and linking the claimed compounds with hot flash treatment.

The specification does not provide citations (commercial or literature) for procuring the starting materials usable that could substitute for the lack of working examples with respect to non-enabled substitutions.

The specification does not disclose biological data for any of the claimed compounds.

The state and the predictability of the art: With regards to making of the compounds, in spite of major advances in protecting group strategies and organic synthesis, the state of the art is unpredictable as to functional group compatibility during many chemical transformations. As such, one of ordinary skill in the art attempting to make applicant's compounds would be faced with trial and error experimentation to arrive at a viable chemistry sequence to introduce the invariants present in the formula. The existence of such unpredictability and uncertainties would prevent one of ordinary skill in the art from accepting the only process present in the specification on its face as universally applicable for all the substitutions claimed.

The quantity of experimentation: For the reasons presented above, there is a

substantial gap between what is taught in the specification and what is being claimed. *Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".*

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recite the limitation effective amount however, no amount has been recited by claims. The claim is indefinite since it is not clear which amount is considered effective in treating hot flashes. Appropriate correction is required.

Claim Rejections - 35 USC § 103

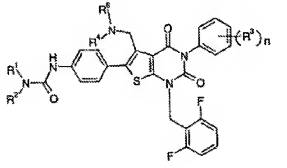
5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,297,379) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94. (Submitted in IDS).

It is noted that Furuya et al. (US 6,297,379) is the National Stage of PCT publication WO00/56739 to Furuya et al. published on September 28, 2000.

Furuya et al. teach a method of treating sex hormone-dependent diseases comprising administering a compound of formula (I):



(I)

where R^6 is:

(abstract).

The compound of formula (I) has excellent gonadotropin releasing horomone (GnRH) antagonizing activity (abstract).

Regarding entering the brain as recited in instant claim 2, it is well known in the art that gonadotropin-releasing hormone (GnRH) is synthesized and released by the hypothalamus and is responsible for the release of follicle stimulating hormone (FSH) and lutenizing hormone (LH) from the anterior pituitary. It is also well known in the art

that the anterior pituitary and hypothalamus are located at the brain stem. As evidenced by Hara et al., the gonadotropin-releasing hormone antagonist, TAK-013, was administered in female cynomolgus monkeys (page 1700). There was an LH surge in the plasma of monkeys treated with vehicle, however, there was no LH surge and LH plasma levels remained low in monkeys treated with TAK-013 (page 1700). Because gonadotropin-releasing hormone is synthesized in the hypothalamus, the gonadotropin-releasing hormone must reach and act in the brain in order to influence the release of lutenizing hormone. Thus it would be obvious that gonadotropin-releasing hormone enters the brain.

Furuya et al. do not specifically teach treating hot flashes, Takayoshi et al. teaches gonadotropin-releasing hormone antagonism and its relation with treatment of hot flashes with such agents (see the whole article and the following paragraph). Takayoshi et al. teach:

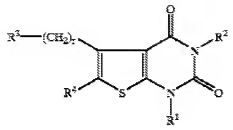
> Gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus and secreted into the portal vein in the median eminence, plays important roles in regulating the menstrual cycle [9] and promoting lordosis behavior [23].

it is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use GNRH in reducing hot flashes by utilizing the compounds disclosed by Furaya et al. One would have been motivated to do so since Furaya et al. disclose that Thienopyridine compounds (which are same as disclosed compounds) possess Gonadotropin-releasing hormone antagonism. As such, the invention as a whole would have been *prima facie* obvious at the time of instant invention.

7. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,048,863) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94. (submitted in IDS).

Furuya et al. teach a method for treating disorders related to gonadotropin releasing hormone (GnRH) comprising administering a thienopyrimidine derivative of the formula:



(abstract).

The thienopyrimidine derivative antagonizes gonadotropin-releasing hormone (column 2, lines 56-57).

Regarding hot flash as recited in instant claim 7, Furuya et al. teach a method of treating disorders related to gondotropin releasing hormone (abstract).

Furuya et al. teach do not specifically teach treating hot flashes, Takayoshi et al. teaches gonadotropin-releasing hormone antagonism and its relation with treatment of hot flashes with such agents (see the whole article and the following paragraph).

Takayoshi et al. teach:

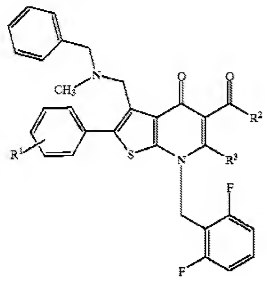
> Gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus and secreted into the portal vein in the median eminence, plays important roles in regulating the menstrual cycle [9] and promoting lordosis behavior [23].

it is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use GNRH in reducing hot flashes by utilizing the compounds disclosed by Furaya et al. One would have been motivated to do so since Furaya et al. disclose that Thienopyridine compounds (which are same as disclosed compounds) possess Gonadotropin-releasing hormone antagonism. As such, the invention as a whole would have been *prima facie* obvious at the time of instant invention.

8. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,001,850) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94 or vice versa. (submitted in IDS).

Furuya et al. teach a method for treating sex hormone dependent diseases comprising administering a thienopyridine derivative having gonadotropin-releasing hormone antagonistic activity of the formula:



(abstract and column 36, lines 5-20).

The thienopyridine derivative has gonadotropin-releasing hormone antagonistic activity (abstract).

Furuya et al. teach do not specifically teach treating hot flashes, Takayoshi et al. teaches gonadotropin-releasing hormone antagonism and its relation with treatment of hot flashes with such agents (see the whole article and the following paragraph).

Takayoshi et al. teach:

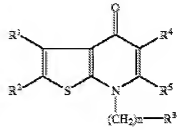
> Gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus and secreted into the portal vein in the median eminence, plays important roles in regulating the menstrual cycle [9] and promoting lordosis behavior [23].

it is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use GNRH in reducing hot flashes by utilizing the compounds disclosed by Furaya et al. One would have been motivated to do so since Furaya et al. disclose that Thienopyridine compounds (which are same as disclosed compounds) possess Gonadotropin-releasing hormone antagonism. As such, the invention as a whole would have been *prima facie* obvious at the time of instant invention.

9. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,187,788) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94 or vice versa. (submitted in IDS).

Furuya et al. teach a method of treating a hormone dependent disease comprising administering a gonadotropin-releasing hormone antagonistic composition comprising a compound of the formula:



(abstract and column 116, lines 30-38).

Furuya et al. teach do not specifically teach treating hot flashes, Takayoshi et al. teaches gonadotropin-releasing hormone antagonism and its relation with treatment of hot flashes with such agents (see the whole article and the following paragraph). Takayoshi et al. teach:

> Gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus and secreted into the portal vein in the median eminence, plays important roles in regulating the menstrual cycle [9] and promoting lordosis behavior [23].

> it is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use GNRH in reducing hot flashes by utilizing the compounds disclosed by Furaya et al. One would have been motivated to do so since Furaya et al.

disclose that Thienopyridine compounds (which are same as disclosed compounds) possess Gonadotropin-releasing hormone antagonism. As such, the invention as a whole would have been *prima facie* obvious at the time of instant invention.

Response to Arguments

10. Applicant's arguments with respect to claims 2-3 and 5-7 have been considered but are moot in view of the new ground(s) of rejection.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call

800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612